CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-986

STATISTICAL REVIEW(S)

/S/

Statistical Review and Evaluation
Clinical Studies

NDA#: 20-986/Class 1S

AUG 20 1999

Applicant: Novo Nordisk Pharmaceuticals Inc.

Name of Drug: NovoLog™ Insulin aspart (Insulin X-14) (recombinant DNA origin)

Indication: Treatment of Diabetes Mellitus

Document Reviewed: Vols. 1.1, 1.110-1.154
Submission dated September 16, 1998

Medical Reviewer: This review has been discussed with the clinical reviewer, Elizabeth Koller M.D. (HFD-510)

Background:

Insulin aspart is an injectable rapid-acting human insulin analog to control postprandial blood glucose and to use in an intensified insulin regimen to improve glycemic control. Insulin aspart is a new molecular entity in which proline is substituted for aspartic acid at position B28. Insulin aspart should be taken immediately before a meal. An application was submitted to the European Medicines Evaluation Agency for review on August 12, 1998.

Controlled Clinical Studies:

The sponsor has submitted the results of 4 active-controlled studies. Three of the studies were in the treatment of type 1 patients and one in the treatment of type 2 patients. One of the type 1 studies was a Phase

2, U.K., multicenter, randomized, double-blind, active-controlled, cross-over study comparing insulin aspart to actrapid (human insulin, HI). All three Phase 3 studies were open-label, parallel-group, active-controlled studies comparing IAsp to HI after 6 months of treatment. After screening, a 4-week run-in period was to ensure that all patients were trained in trial procedures and on a multiple-injection treatment regimen with HI as meal related insulin and Neutral Protamine Hagedorn (NPH) as basal insulin. Two of the Phase 3 studies were on type 1 patients one conducted in Europe (35) and the other in the U.S. and Canada (36) which included an extension trial with a total treatment period of one year. The type 2 trial (37) which enrolled fewer patients than the type 1 trials, was conducted in the U.S with no extension period. The 4 studies were summarized in Table 1. This review discusses the 3 phase 3 trials.

Table 1. Brief Summary of Controlled Trials

Study ID	# of Cntrs	Total Sample Size	Type of Study & Control	Design primary variable	Duration of Treatment
ANA/DCD/025/UK 4/7/95-11/14/95	10	Type 1 104 randomized diabetic males 1. Insulin aspart 2. Actrapid Human Insulin 100 U/ml	Phase 2b, Cross-over, active-controlled	multicenter, randomized double-blind fructosamine	run-in 4 wks 2 treatment period of 4 wks each
ANA/DCD/035/EU	93	Type 1 n 1. 100 U/ml Insulin Aspart, s.c., immediately before main meal 708 2. 100 U/ml Actrapid Human Insulin, s.c. 30 minutes before meal 362	Phase 3, active-controlled	multicenter. multinational, randomized parallel-group, open-label HbA_{1c}	6 months
ANA/DCD/036/USA/ Canada	59	Type 1 n 1. 100 U/ml Insulin aspart s.c. 597 2. 100 U/ml Human Insulin, s.c. 287	Phase 3, active-controlled	multicenter, randomized, parallel, open-label HbA_{1c}	6 months
ANA/DCD/037/US	17	Type 2 n 1. 100 U/ml Iasp, s.c. 91 2. 100 U/ml HI s.c. 91	Phase 3, active-controlled	multicenter, randomized parallel, open-label HbA_{1c}	6 months

Protocol Summary of Phase 3 Studies (35, 36, & 37)

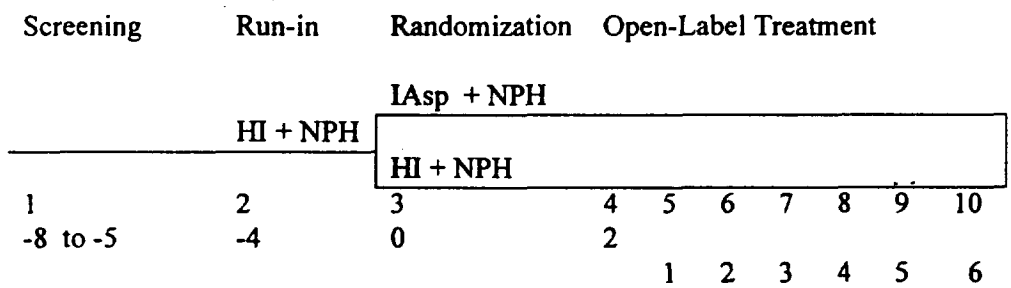
The primary objective of the phase 3 trials was to compare the effect of IAsp with HI on glycemic control as measured by HbA_{1c}.

The secondary objectives were to compare IAsp with HI after 6 months of treatment in 1)the effect on 8-point BG profiles, 2) the incidence of hypoglycemic episodes 3) the safety profile and 4) the safety profile as measured by standard safety parameters (hematology, biochemistry), lipids, antibodies to IAsp and HI and fundus-photography (at selected sites).

The 2 multicenter, multinational trials in type 1 diabetic patients randomized patients in a 2:1 ratio of IAsp to HI. The US multicenter study in patients with type 2 diabetes randomized patients in a 1:1 ratio of IAsp to HI.

The trials included a screening visit to assess eligibility, a 4-week run-in period to ensure that all subjects were on a multiple-injection treatment regimen with HI as meal related insulin and Neutral Protamine Hagedorn (NPH) as basal insulin, administered once or twice daily. The treatment period after randomization was 6 months.

The trial scheme is presented in the following diagram:



HbA_{1c} was assessed at Visits 1 (screening), 3 (randomization), 7 (month 3), and 10 (month 6). The 8-point profile BG was assessed at Visits 3, 9 and 10. Antibody assessments were at baseline and month 6 for Study 35 and an additional assessment at month 3 for Studies 36 and 37. Patients who completed the trial were asked to participate in a 2.5-year extension trial in Study 35 and a 6-month extension trial in Study 36.

Hypoglycemic episodes

Patients were instructed to record hypoglycemic episode in their diary. In Study 35, the definitions of minor and major hypoglycemic episodes were as follows:

Minor: The subjects dealt with the episode themselves

Major: A: The subject required third party help
B: The subject required i.v. glucose or glucagon treatment

For Study 37, the definitions were as follows:

Minor (mild to moderate): symptoms of hypoglycemia(sweating, strong hunger, dizziness, tremor, etc.); and/or a glucose meter measurement of a blood glucose value below 45 mg/dl.

Major (severe): symptoms of hypoglycemia with severely impaired consciousness that requires assistance of another person and hospitalization.

For the major events it is recorded as whether the patient required third party help (Major A) or the patient required i.v. glucose or glucagon treatment (Major B).

For Study 36, the definition was changed from the former (Study 35) to the latter (Study 37) definition in the Note of Administrative Change (dated 12/20/96).

In Studies 36 Amendment 2 (4/08/97) and 37 Amendment 3 (4/01/97), the once daily basal NPH in run-in was amended to "an addiaional breakfast dose of Insulin NPH may be added to the treatment at the investigator's discretion" if satisfactory control cannot be attained with once a day Insulin NPH for the patient. In addition, the run-in period can be extended from 4 weeks ± 3 days to 5 weeks ± 3 days to attain the added requirement that the patient must have been on the same NPH insulin regimen for at least one week prior to the randomization at visit 3. Also, the amendment added that the number and timing of Insulin NPH injections should not be changed after randomization.

Studies 35 and 36 included type 1 diabetic patients 18 years or older with a body mass index (BMI) ≤35.0 kg/m^2 and a HbA_{1c} ≤11.0%. For Study 37, it included type 2 diabetic patients 35 years or older with a BMI ≤40.0 kg/m^2 and a HbA_{1c} ≤11%.

Treatment

During the treatment period, HI or IAsp was administered as meal-time insulin. Patients were advised that HI was to be injected 30 minutes before the meal, while IAsp was to be injected immediately before the meal. Insulin dosage was adjusted throughout the trial according to local practice, based on the subjects self-measured BG and the between-visit-8-point BG profiles, aiming at the following targets for glycemic control.

fasting/preprandial BG:	5.0-8.0 mmol/l (90-144 mg/dl)
postprandial BG (1 to 3 hours after a meal):	≤10 mmol/l (≤180 mg/dl)
2:00 a.m. BG:	5.0-8.0 mmol/l (90-144 mg/dl)

Patients were asked to record the self-monitoring BG in a diary but these data were not recorded in the CRFs.

Patients treated with IAsp were advised that an increase in their basal insulin requirements might occur during treatment with IAsp.

Efficacy Variables

The primary efficacy outcome was HbA_{1c} at month 6. The secondary endpoints were derived from the 8-point BG profiles after 6 months of treatment. The prandial BG increment after 3 meals was defined as the mean difference between the BG value 90 minutes after the meal and the BG value just before the meal, over the 3 meals. The variability of the 8-point BG profile was defined as the standard deviation of the BG values at the eight time points for each subject.

The sponsor also conducted analysis on ratio of meal-related insulin to basal insulin and the total amount of meal-related insulin and basal insulin at the end of the 6-month treatment period.

Patient Disposition and Baseline Characteristics

Study 35

Of the 1237 patients screened, a total of 1070 patients were randomized in 88 centers in Europe with 708 patients to the IAsp treatment group and 362 to the HI treatment group (2 to 1 ratio). The disposition of patients is displayed in Table 2.

Table 2 Disposition of Patients – Study 35

Patient Status	IAsp	HI	Total
Screened			1237
Randomized	708	362	1070
Intent to Treat	698	349	1047 (98%)
Completed	676 (96%)	335 (94%)	1011 (95%)
Withdrawals	32 (4.5%)	27 (7.5%)	59 (5.5%)
Adverse Event	6	3	9
Lack of Efficacy	5	3	8
Non-compliance	3	6	9
Other	18	15	33
Per-Protocol	674 (95%)	332 (93%)	1006 (94%)

Patients were ~38 years of age with 99% Caucasians and 55% men. The mean weight is ~ 74 kg with a BMI of ~25 kg/m^2. Table 3 summarizes patients' diabetic history.

Table 3 Baseline Diabetic Characteristics of Patients – Study 35

	IAsp	HI
N	707	358
Duration of Diagnosed Diabetes (yrs)		
Mean (SD)	14.7 (10.1)	15.0 (10.1)
Median	12.6	13.1
Min - Max		
Important Baseline Variables		
HbA1c (%)		
Mean (SD)	7.96 (1.16)	7.98 (1.17)
Median	8	7.95
Min - Max		
Number of Daily Basal Injections		
0 or Unknown N (%)	4 (1%)	2 (1%)
1 N (%)	414 (59%)	221 (62%)
2 N (%)	287 (41%)	135 (38%)
3 N (%)	2 (<1%)	

Study 36

A total of 884 patients were randomized in 59 centers in US (48) and Canada (11) with a 2 to 1 ratio of 597 patients in the IAsp group and 287 patients in the HI group. Table 4 displays patient disposition and Table 5, patient diabetic history.

Table 4 Disposition of Patients – Study 36

Patient Status	IAsp	HI	Total	
Screened			1102	
Screening Failures			166	
Withdrawals in Run-in Period			52	
Randomized	597	287	884	
Exposed	596	286	882	
Withdrawals in Treatment Period				
Adverse Event	3	2	5	0.60%
Ineffective Therapy	3	1	4	0.50%
Non-compliance	9	2	11	1.20%
Other	30	19	49	5.60%
Total	45	24	69	7.80%
Completed Trial	552 (93%)	263 (92%)	815 (92%)	
Efficacy Populations				
Intention to treat	587	279	866	98%
Per-Protocol	546	257	803	91%

The mean age of patients was ~39 with ~52% men and 94% Caucasians. The mean weight of patients were 75.6 kg and the mean BMI were 25.6 kg/m^2.

Table 5 Baseline Diabetic Characteristics of Patients – Study 36

	IAsp	HI
N	596	286
Duration of Diagnosed Diabetes (yrs)		
Mean (SD)	15.7 (9.7)	15.8 (9.3)
Median	14.4	14.6
Min - Max		
Important Baseline Variables		
HbA1c (%)		
Mean (SD)	7.90 (1.13)	7.95 (1.25)
Median	7.8	7.9
Min - Max		
Number of Daily Basal Injections		
0 or Unknown N (%)	5 (1%)	3 (1%)
1 N (%)	573 (96%)	272 (95%)
2 N (%)	18 (3%)	11 (4%)

Study 37

Of the 252 patients screened, 191 were enrolled in the 4-5 week run-in period. Nine patients withdrew during the run-in period. Thus, a total of 182 patients were randomized 91 to the IAsp group and 91 to the HI group. Five (1, IAsp & 4, HI) randomized patients who had no efficacy data after baseline visit were excluded from the ITT population (177). Seven patients did not complete the study and were therefore excluded from the completers population (170). The Per-Protocol (PP) population (156) excluded further 14 patients with protocol violations as displayed in Table 6.

Table 6 Disposition of Patients – Study 37

Patient Status	IAsp	HI	Total
Screened			252
Randomized	91	91	182
Intent to Treat	90	87	177 (97%)
Completed	88	82	170 (93%)
Withdrawals	3	9	12
Adverse Event	0	3	3
Lack of Efficacy	0	1	1
Non-compliance	1	1	2
Other	2	4	6
Per-Protocol	78	78	156 (86%)

The baseline diabetic characteristics are summarized in Table 7 for randomized patients. Mean HbA_{1c} were different between the two treatment groups (8.11%, IAsp vs. 7.87%, HI).

Table 7 Baseline Diabetic Characteristics of Patients – Study 37

	IAsp	HI
N	91	91
Duration of Diagnosed Diabetes (yrs)		
Mean (SD)	12.7 (7.7)	12.9 (8.0)
Median	10.5	11.1
Min - Max		
Important Baseline Variables		
HbA1c (%)	91	91
Mean (SD)	8.11 (1.18)	7.87 (1.11)
Median	8.2	7.8
Min - Max		
Number of Daily Basal Injections		
0 or Unknown N (%)	1 (1%)	2 (2%)
1 N (%)	87 (96%)	85 (93%)
2 N (%)	3 (3%)	4 (4%)
3 N (%)	18 (3%)	11 (4%)

Efficacy Evaluation

The analysis of the primary endpoint HbA_{1c} was based on both the ITT population and the PP population. The analysis of covariance model included effects of treatment and center with baseline HbA_{1c} as covariate. The least squared means (LSM) of HbA_{1c} and the treatment difference with its confidence intervals are displayed in Tables 8-10. For all 3 studies, the analyses based on the two populations (ITT, PP) were consistent. The treatment differences in HbA_{1c} at month 6 between IAsp and HI were -0.12% -0.16% and -0.14%, for studies 35, 36, and 37, respectively.

Table 8 HbA_{1c} (%) over Time – Study 35 (Type 1, Europe)

	IAsp			HI			Difference		95% C.I.		p
ITT	n	LSM	SE	n	LSM	SE	LSM	SE	Lower	Upper	
Baseline	697	7.95	0.04	346	7.94	0.06	0.01	0.07	-0.13	0.15	0.91
Month 3	688	7.86	0.03	341	7.92	0.04	-0.06	0.04	-0.15	0.03	0.18
Month 6	688	7.87	0.03	343	8.00	0.04	-0.13	0.05	-0.22	-0.03	0.01
PP											
Baseline	673	7.96	0.04	329	7.91	0.06	0.04	0.07	-0.10	0.19	0.55
Month 3	674	7.85	0.03	332	7.92	0.04	-0.07	0.04	-0.16	0.02	0.11
Month 6	673	7.87	0.03	330	7.99	0.04	-0.12	0.05	-0.22	-0.02	0.02

Table 9 HbA_{1c} (%) over Time – Study 36 (Type 1, N. America)

	IAsp			HI			Difference		95% C.I.		p
ITT	n	LSM	SE	n	LSM	SE	LSM	SE	Lower	Upper	
Baseline	586	7.90	0.06	279	7.95	0.08	-0.06	0.08	-0.22	0.11	0.49
Month 3	569	7.66	0.04	271	7.77	0.05	-0.11	0.05	-0.21	-0.01	0.03
Month 6	576	7.76	0.04	271	7.92	0.05	-0.16	0.05	-0.26	-0.05	<0.01
PP											
Baseline	544	7.88	0.06	257	7.96	0.08	-0.09	0.09	-0.25	0.08	0.32
Month 3	543	7.65	0.04	255	7.76	0.05	-0.11	0.05	-0.22	-0.01	0.04
Month 6	543	7.76	0.04	257	7.92	0.05	-0.16	0.06	-0.27	-0.05	<0.01

Table 10 HbA_{1c} (%) over Time – Study 37 (Type 2)

	IAsp			HI			Difference		95% C.I.		p
ITT	n	LSM	SE	n	LSM	SE	LSM	SE	Lower	Upper	
Baseline	89	8.11	0.14	87	7.87	0.14	0.25	0.17	-0.08	0.58	0.14
Month 3	88	7.62	0.11	85	7.77	0.10	-0.15	0.13	-0.40	0.10	0.24
Month 6	89	7.74	0.11	85	7.83	0.11	-0.09	0.13	-0.34	0.17	0.50
PP											
Baseline	77	8.06	0.15	78	7.80	0.15	0.26	0.18	-0.10	0.61	0.15
Month 3	78	7.55	0.10	78	7.73	0.10	-0.18	0.12	-0.42	0.06	0.14
Month 6	78	7.71	0.11	78	7.85	0.11	-0.14	0.13	-0.40	0.12	0.30

Figure 1 displays the mean HbA_{1c} levels during the course of the study from screening (-1) to month 6. Figure 2 displays the mean change from baseline in HbA_{1c} during the study.

Figure 1 Mean HbA_{1c} Levels from Screening to Month 6 – Studies 35, 36, & 37

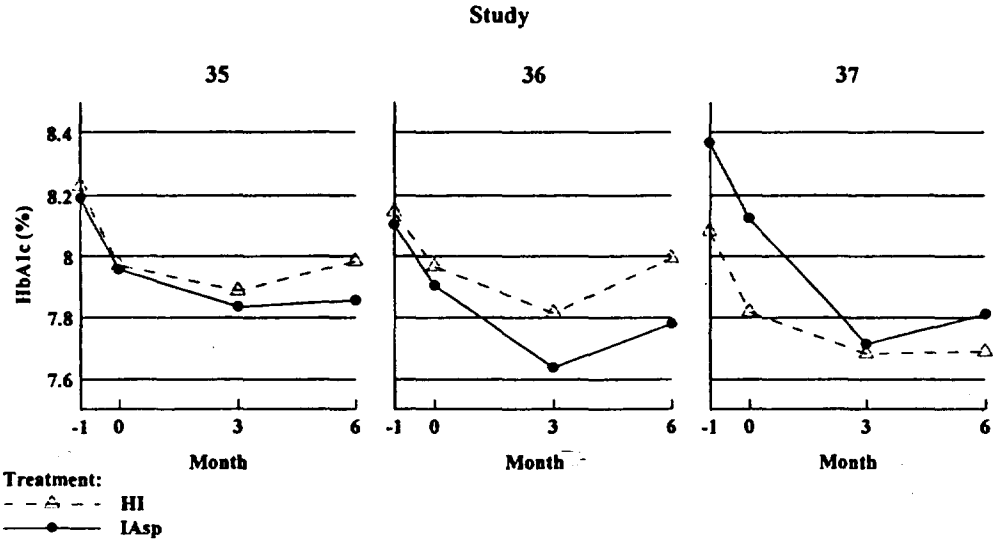
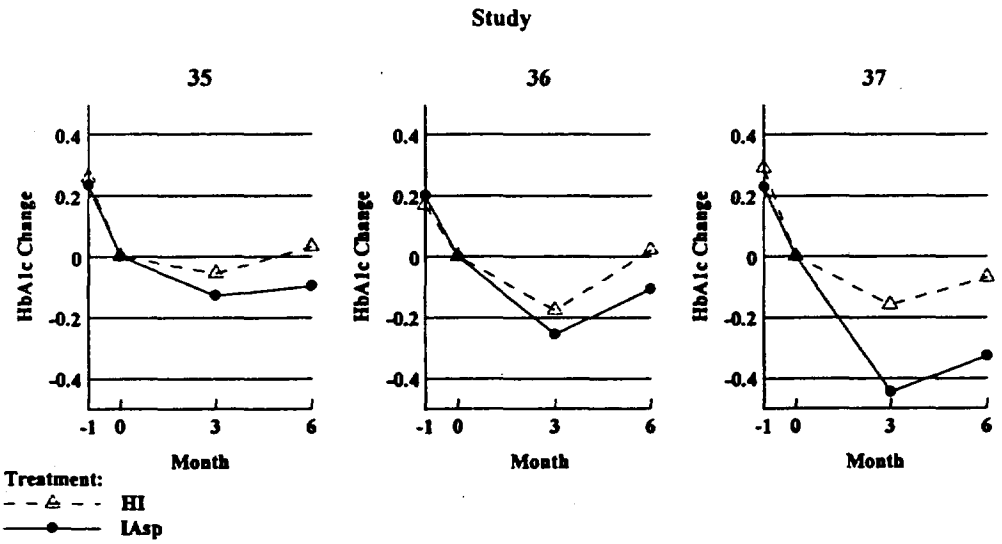


Figure 2 Mean HbA_{1c} Change from Baseline by Time – Studies 35, 36, & 37



Secondary Efficacy

For the month 6 glucose profile analysis of covariance with treatment, center in the model and baseline as covariate, the results are displayed in Tables 11-13 for Studies 35, 36, and 37, respectively and Figure 3. For Studies 35 and 36, after 6 months treatment, the blood glucose levels at 90 minutes after each of the 3 meals were significantly lower for the IAsp treated patients than the HI treated patients. For before meals, the blood glucose level was higher in the IAsp group (significantly in 35 but not in 36) for breakfast. The before lunch blood glucose was lower in the IAsp treated patients (significantly in 36 but not in 35). The before dinner blood glucose was significantly higher for IAsp treated patients in both studies. For Study 37, the 8-point blood glucose at month 6 was not significantly different between the two treatment groups.

Table 11 Eight-point Blood Glucose (mmol/l) Analysis after 6 Months – Study 035

Time of Day	IAsp			HI			Difference	95% C.I.		p
	n	LSM	SE	n	LSM	SE	LSM	Lower	Upper	
Before Breakfast	672	**8.46**	0.13	337	**7.68**	0.18	**0.79**	[0.36	1.21]	<0.01
90 min after Breakfast	669	**8.87**	0.15	331	**10.06**	0.21	**-1.20**	[-1.68	-0.71]	<0.01
Before Lunch	671	**7.13**	0.13	336	**7.31**	0.18	**-0.18**	[-0.60	0.23]	0.38
90 min after Lunch	667	**7.96**	0.12	333	**8.51**	0.17	**-0.55**	[-0.96	-0.15]	0.01
Before Dinner	672	**7.99**	0.13	337	**7.30**	0.18	**0.69**	[0.25	1.13]	<0.01
90 Min after Dinner	664	**8.35**	0.14	334	**8.98**	0.19	**-0.63**	[-1.07	-0.18]	0.01
Bedtime	670	**8.71**	0.14	336	**8.68**	0.19	**0.04**	[-0.42	0.49]	0.87
2 am	647	**8.44**	0.14	325	**8.05**	0.19	**0.39**	[-0.05	0.83]	0.08

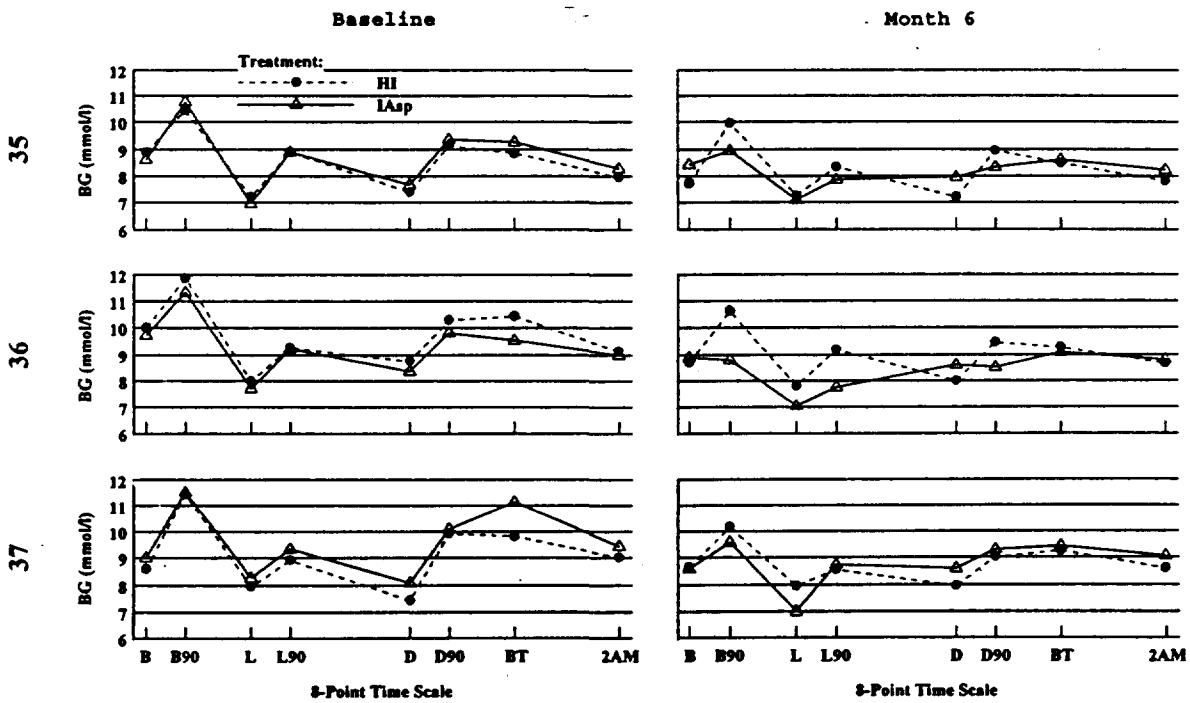
Table 12 Eight-point Blood Glucose (mmol/l) Analysis after 6 Months – Study 036

Time of Day	IAsp			HI			Difference	95% C.I.		p
	n	LSM	SE	n	LSM	SE	LSM	Lower	Upper	
Before Breakfast	558	**8.82**	0.18	262	**8.53**	0.25	**0.28**	[-0.28	0.85]	0.33
90 min after Breakfast	556	**8.67**	0.19	261	**10.33**	0.26	**-1.66**	[-2.25	-1.06]	0.00
Before Lunch	558	**7.01**	0.17	262	**7.65**	0.23	**-0.65**	[-1.17	-0.12]	0.02
90 min after Lunch	556	**7.60**	0.17	260	**9.00**	0.23	**-1.40**	[-1.93	-0.87]	<0.01
Before Dinner	558	**8.59**	0.17	261	**7.89**	0.24	**0.70**	[0.16	1.25]	0.01
90 Min after Dinner	555	**8.48**	0.17	261	**9.33**	0.23	**-0.85**	[-1.38	-0.32]	<0.01
Bedtime	557	**8.99**	0.18	260	**9.04**	0.25	**-0.05**	[-0.62	0.52]	0.87
2 am	555	**8.67**	0.18	258	**8.44**	0.25	**0.24**	[-0.33	0.81]	0.41

Table 13 Eight-point Blood Glucose (mmol/l) Analysis after 6 Months – Study 037

Time of Day	IAsp			HI			Difference	95% C.I.		p
	n	LSM	SE	n	LSM	SE	LSM	Lower	Upper	
Before Breakfast	87	8.52	0.28	84	8.78	0.29	-0.26	[-1.03	0.52]	0.51
90 min after Breakfast	87	9.65	0.37	83	10.36	0.38	-0.71	[-1.73	0.30]	0.17
Before Lunch	87	7.03	0.34	84	7.90	0.34	-0.87	[-1.80	0.06]	0.07
90 min after Lunch	87	8.68	0.32	82	8.64	0.33	0.04	[-0.84	0.91]	0.93
Before Dinner	87	8.52	0.38	83	7.96	0.39	0.55	[-0.50	1.61]	0.30
90 Min after Dinner	87	9.14	0.41	83	9.21	0.42	-0.08	[-1.19	1.04]	0.89
Bedtime	86	9.35	0.35	83	9.46	0.36	-0.11	[-1.09	0.87]	0.83
2 am	86	8.97	0.37	82	8.72	0.38	0.25	[-0.76	1.27]	0.62

Figure 3 Profile of 8-Point Blood Glucose Levels at Baseline and Month 6 by Studies



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Prandial BG increment

The prandial BG increment was evaluated as the mean difference between pre- and post-meal BG values averaged over the three meals. The analysis of covariance using baseline prandial BG increment as covariate for the 3 studies is displayed in Table 14. The analysis included patients with both baseline and month 6 data on prandial BG increment.

Table 14 Prandial BG Increment (mmole/l) Analysis - Studies 35, 36, & 37

Study #	IAsp		HI		Difference		95% C.I.		p
	LSM	SE	LSM	SE	LSM	SE	Lower	Upper	
#35	n=580		n=287						
Baseline	1.86	0.11	1.61	0.14	0.26	0.17	-0.07	0.59	0.13
Month 6	**0.54**	0.10	**1.61**	0.13	**-1.07**	0.15	-1.37	-0.77	**<0.01**
#36	n=476		n=224						
Baseline	1.61	0.15	1.67	0.20	-0.05	0.22	-0.48	0.37	0.80
Month 6	**0.08**	0.14	**1.48**	0.18	**-1.40**	0.20	-1.79	-1.01	**<0.01**
#37	n=70		n=68						
Baseline	2.13	0.27	2.51	0.27	-0.38	0.35	-1.07	0.30	0.27
Month 6	**1.73**	0.24	**1.52**	0.24	**0.21**	0.31	-0.40	0.82	**0.50**

At month 6, the prandial BG increment was significantly less in the IAsp treated patients than the HI treated patients for studies 35 and 36. For the type 2 patients (Study 37), the increment was not significantly different between the two treatment groups.

Variability of the 8-Point Blood Glucose Profile

The BG variability was defined as the within-subject standard deviation of the eight BG measurements. Table 15 summarizes the analysis of covariance with treatment and center as the fixed factors and baseline within-subject standard deviation as covariate. The analysis included patients with both baseline and month 6 data for the within-subject standard deviation. The BG variability was not significantly different at month 6 between the treatment groups for all 3 studies.

Table 15 Blood Glucose Variability Analysis - Studies 35, 36, & 37

Study #	IAsp		HI		Difference		95% C.I.		p
	LSM	SE	LSM	SE	LSM	SE	Lower	Upper	
#35	n=535		n=266						
Baseline	3.33	0.06	3.21	0.08	0.12	0.10	-0.07	0.31	0.21
Month 6	**2.69**	0.06	**2.73**	0.07	**-0.03**	0.09	-0.20	0.14	**0.70**
#36	n=459		n=205						
Baseline	3.97	0.09	4.05	0.11	-0.08	0.12	-0.32	0.16	0.50
Month 6	**3.18**	0.08	**3.35**	0.11	**-0.16**	0.11	-0.38	0.05	**0.14**
#37	n=66		n=64						
Baseline	3.24	0.19	3.05	0.19	0.18	0.24	-0.29	0.66	0.44
Month 6	**2.65**	0.17	**2.81**	0.17	**-0.16**	0.21	-0.59	0.27	**0.46**

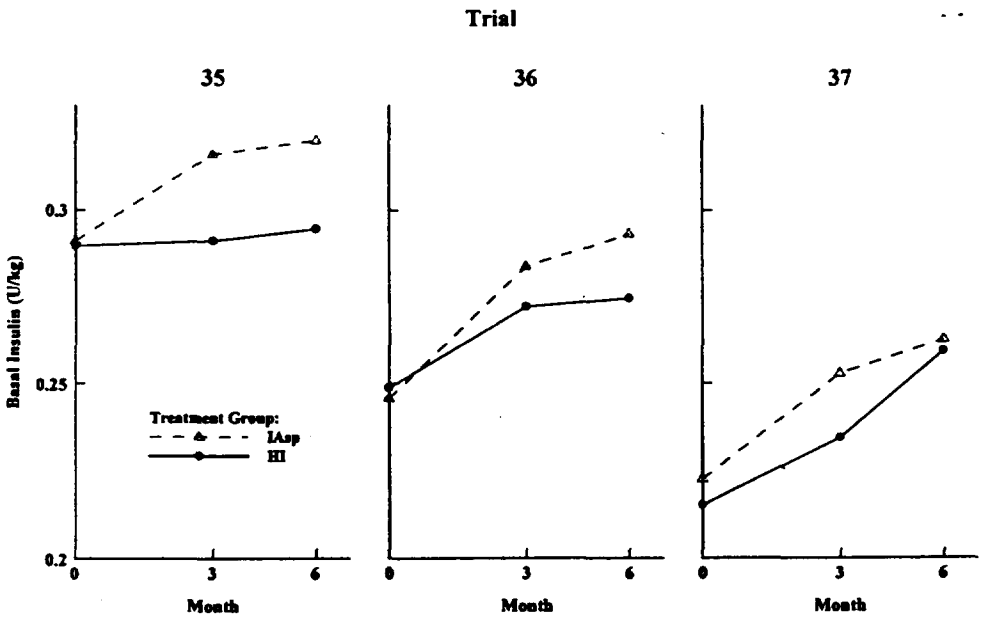
Basal Insulin-dose

The analysis of covariance for basal insulin measurement at month 6 using baseline basal insulin dose as covariate is displayed in Table 16 For studies 35 and 36, the basal insulin dose increased significantly for the IAsp treated patients compared to the HI treated patients. For study 37, the basal insulin was not significantly different at month 6 for the two treatment groups. Figure 4 displays the mean levels of basal insulin by treatment groups over time for the PP population.

Table 16 Covariance Analysis of Basal Insulin (U/kg) at Month 6 - Studies 35, 36, & 37

Study #	IAsp		HI		Difference		95% C.I.		p
	LSM	SE	LSM	SE	LSM	SE	Lower	Upper	
#35	n=682		n=341						
Baseline	0.2886	0.0047	0.2909	0.0063	-0.0023	0.0074	-0.0168	0.0123	0.76
Month 6	**0.3194**	0.0026	**0.2932**	0.0036	**0.0262**	0.0042	0.0180	0.0343	**<0.01**
#36	n=563		n=260						
Baseline	0.2443	0.0065	0.2551	0.0086	-0.0108	0.0089	-0.0282	0.0066	0.22
Month 6	**0.2958**	0.0045	**0.2736**	0.0059	**0.0222**	0.0061	0.0101	0.0342	**<0.01**
#37	n=85		n=84						
Baseline	0.2265	0.0150	0.2171	0.0150	0.0093	0.0177	-0.0256	0.0442	0.60
Month 6	**0.2566**	0.0108	**0.2515**	0.0108	**0.0051**	0.0127	-0.0200	0.0302	**0.69**

Figure 4 Mean Basal Insulin Levels (U/kg) over Time – Studies 35, 36, & 37



Binary Analysis on Basal Insulin Change

At month 6, the increase or decrease of basal insulin from baseline was dichotomized. The proportions of patients in the two categories were compared between the IAsp group and HI group in Table 17.

Table 17 Binary Analysis of Basal Insulin (U/kg) at Month 6 - Studies 35, 36, & 37

Study #	IAsp		HI		p
Basal Insulin Change	n	%	n	%	
#35	689		345		
≤0	214	31%	163	47%	
>0	475	**69%**	182	**53%**	**<0.01**
#36	580		271		
≤0	158	27%	422	42%	
>0	422	**73%**	157	**58%**	**<0.01**
#37	85		89		
≤0	25	28%	22	26%	
>0	64	**72%**	63	**74%**	**0.74**

Proportions of patients with >0 basal insulin change from baseline were significantly greater in the IAsp treatment group than the HI group for study 35 (69% vs. 53%) and study 36 (73% vs. 58%). For study 37, the 2 proportions were not different (72% vs. 74%).

Meal Insulin Dose

The meal insulin dose at month 6 was not significantly different between treatment groups when adjusted for center and the baseline meal insulin dose as covariate (Table 18).

Table 18 Covariance Analysis of Meal Insulin (U/kg) at Month 6 - Studies 35, 36, & 37

Study #	IAsp		HI		Difference		95% C.I.		p
	LSM	SE	LSM	SE	LSM	SE	Lower	Upper	
#35	n=682		n=341						
Baseline	0.4000	0.0060	0.4053	0.0082	-0.0053	0.0096	-0.0241	0.0135	0.58
Month 6	**0.3920**	0.0041	**0.3957**	0.0056	**-0.0037**	0.0065	-0.0165	0.0091	**0.57**
#36	n=563		n=260						
Baseline	0.4155	0.0078	0.4213	0.0103	-0.0058	0.0106	-0.0267	0.0151	0.58
Month 6	**0.4114**	0.0061	**0.4070**	0.0079	**0.0045**	0.0082	-0.0117	0.0206	**0.59**
#37	n=85		n=84						
Baseline	0.3623	0.0231	0.3730	0.0232	-0.0106	0.0273	-0.0646	0.0433	0.70
Month 6	**0.4111**	0.0154	**0.4398**	0.0154	**-0.0287**	0.0181	-0.0645	0.0070	**0.11**

For total insulin at month 6, the results were similar to the basal insulin results; total insulin dose increased significantly in the IAsp group than the HI group for studies 35 and 36 but no difference between groups for study 37. Similarly, the ratio of meal to basal insulin was significantly different between IAsp group and HI group in studies 35 and 36 but not in study 37.

Analysis on HbA_{1c} and basal insulin change from baseline

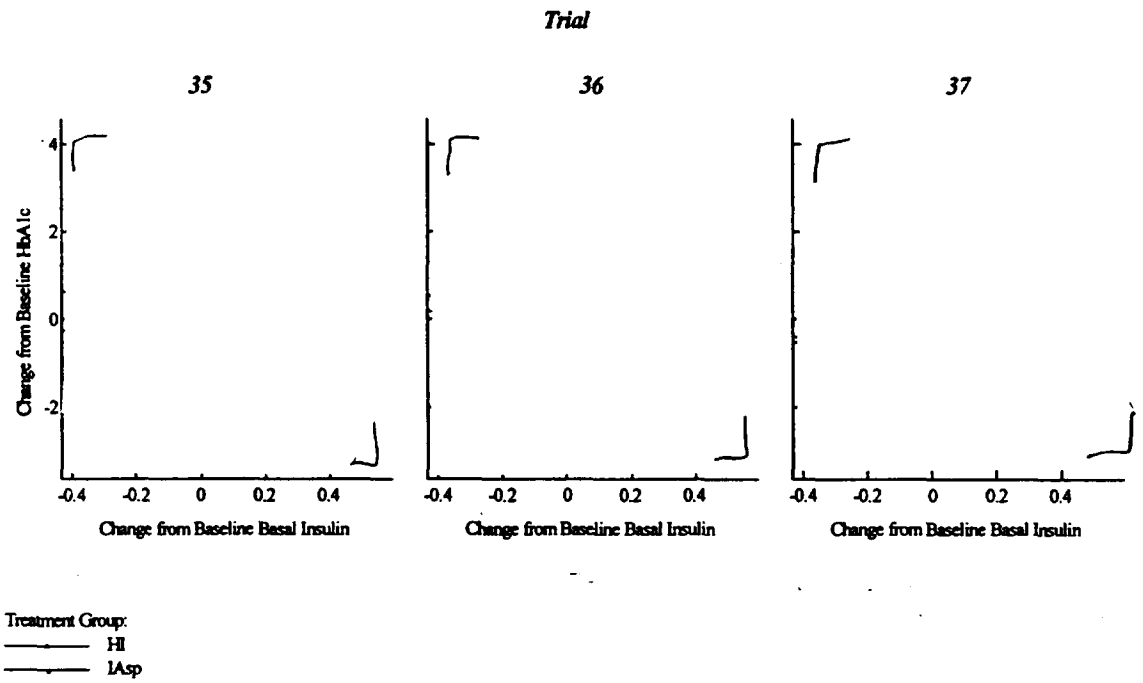
At month 6, change from baseline HbA_{1c} and change from baseline basal insulin were examined. First the model only included treatment factor in the model. The p-values for treatment was significant for studies 35 and 36 (p=0.015 & p=0.025) but not study 37 (p=0.15). Then the covariate, change from baseline basal insulin, was added in the model. The p-values for treatment factor were p=0.062, p=0.052 and p=0.222, respectively, for studies 35, 36 and 37 (Table 19).

Table 19 HbA_{1c} Change from Baseline and Basal Insulin (U/kg) Adjustment at Month 6

Study #	IAsp		HI		Difference		95% C.I.		p
Basal Insulin Change	LSM	SE	LSM	SE	LSM	SE	Lower	Upper	Trt
#35									
No adjustment	-0.10	0.03	0.03	0.04	-0.13	0.05	-0.23	-0.03	0.015
Adjustment	-0.10	0.03	0.00	0.04	-0.10	0.05	-0.20	0.00	0.062
#36									
No adjustment	-0.12	0.03	0.02	0.05	-0.14	0.06	-0.26	-0.02	0.025
Adjustment	-0.11	0.03	0.01	0.05	-0.12	0.06	-0.24	0.00	0.052
#37									
No adjustment	-0.30	0.10	-0.10	0.10	-0.20	0.14	-0.48	0.07	0.151
Adjustment	-0.28	0.10	-0.11	0.10	-0.18	0.14	-0.46	0.11	0.222

Figure 5 displays at month 6, the HbA_{1c} change from baseline by the change of basal insulin. The interaction between treatment and change from baseline basal insulin dose was significant in study 35 (p<0.01), marginal for study 36 (p=0.17) and not significantly different in study 37 (p=0.72). For studies 35 and 36, the regression line indicates that for IAsp patients, the decrease in HbA_{1c} from baseline is associated with the increase in basal insulin from baseline.

Figure 5 Change from Baseline to Month 6 HbA_{1c} by Basal Insulin Change



The descriptive statistics in change from baseline HbA_{1c} for patients with basal insulin dose increased or not increased from baseline are displayed in Table 20.

Table 20 Descriptive Statistics of HbA_{1c} Change from Baseline to Month 6 by Basal Insulin

Study	Increase of basal insulin	IAsp n	IAsp Mean	IAsp Std Dev	HI n	HI Mean	HI Std Dev
#35	No	213	**-0.03**	0.78	161	**0.07**	0.81
	Yes	474	**-0.13**	0.79	179	**-0.01**	0.80
#36	No	157	**-0.01**	0.84	114	**0.02**	0.80
	Yes	418	**-0.16**	0.84	157	**0.02**	0.83
#37	No	25	**-0.28**	0.84	22	**-0.24**	0.96
	Yes	63	**-0.31**	1.09	63	**-0.06**	0.74

Conclusion on Efficacy Variable HbA_{1c}

The sponsor claims HbA_{1c} control was superior with IAsp than with HI after 6 months of treatment in patients with Type 1 diabetes. The sponsor's claim of superiority (the original hypothesis involved testing for non-inferiority) is not acceptable because of the following:

1. The HbA_{1c} difference at month 6 between IAsp and HI were -0.13% and -0.16% for study 35 and study 36, respectively, which is small and clinically insignificant according to the Medical Officer, even though it was statistically significant.

2. In the first comment of a Consultation dated August 1, 1997, this reviewer addressed the sponsor's reversal of the original intent not to test superiority after establishing the "non-inferiority". It was pointed out that "...the claim superiority of the test drug may reflect the large sample size even if the difference is not clinically meaningful." In a response to our first comment, the sponsor in a letter dated September 22, 1997, decided to change the procedure back to evaluating effectiveness of IAsp to "non-inferior" to HI. The sample size role is verified in study 37, which is 20% or less in size of study 35 and study 36. Though the magnitude of the estimate in study 37 was similar (-0.14%) to studies 35 and 36 (-0.12, -0.16), it was not statistically significant (p=0.30).

3. Compared to the HI-treated patients, basal insulin dose increased significantly in the IAsp-treated patients whereas the meal insulin dose was not statistically different between groups. Although the sponsor claims "the observed treatment difference in HbA_{1c} was not due to differences in basal insulin doses", the sensitivity analysis does not support the sponsor's claim. It appears that the HbA_{1c} reduction is associated with the increase of basal insulin dose from baseline in the IAsp group but not in the HI group...

4. In these active-controlled, open-label studies, it is important to avoid bias in the trial conduct. In section 4.5.1 of the study report of all 3 studies, it was stated that "Subjects receiving IAsp were advised that an increase in their basal insulin requirements might occur during treatment with IAsp." This advice might introduce bias in favor of IAsp-treated patients than HI-treated patients in term of glycemic control.

Major Hypoglycemia

The data on major hypoglycemia was based on the sponsor's definition in the protocol. The Medical Officer, Dr. Koller, defines a major hypoglycemic event with a blood glucose of 2 mmole/l or less. The blood glucose level was missing in more than 50% of the Major B events. Thus, the analysis on major hypoglycemia is based on the sponsor's definition.

The number of subjects who experienced at least one major hypoglycemia episode is summarized in Table 21 for run-in (4-week) period and the 6-month treatment period. In studies 35 and 36, 15% to 19% of patients experienced at least one major hypoglycemic episode during the treatment period. For study 37 it was 10% in the IAsp group and 5% in the HI group.

Table 21 Major Hypoglycemic Events during Run-In and Treatment Period

Study	35				36				37			
	IAsp n=707		HI n=358		IAsp n=596		HI n=286		IAsp n=91		HI n=91	
Major A & B	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
run-in	44 (6%)	70	21 (6%)	30	44 (7%)	86	20 (7%)	42	1 (1%)	1		
Treatment	**109 (15%)**	**312**	**64 (18%)**	**151**	**104 (17%)**	**265**	**54 (19%)**	**155**	**9 (10%)**	**12**	**5 (5%)**	**8**
Major A												
Run-in	38 (5%)	62	16 (4%)	25	38 (6%)	79	19 (7%)	41	1 (1%)	1		
Treatment	**97 (14%)**	**272**	**51 (14%)**	**126**	**93 (16%)**	**239**	**49 (17%)**	**144**	**9 (10%)**	**11**	**4 (4%)**	**7**
Major B												
Run-in	6 (<1%)	8	5 (1%)	5	6 (1%)	7	1 (<1%)	1				
Treatment	**20 (3%)**	**40**	**16 (4%)**	**25**	**22 (4%)**	**26**	**7 (2%)**	**11**	**1 (1%)**	**1**	**1 (1%)**	**1**

n: number of subjects with a major episode
E: number of episodes

Percents of patients in number of major event categories, 0, 1, 2, 3, and ≥4 are displayed in Table 22.

Table 22 Percent of Patients with 0, 1, 2, 3 , & ≥4 Major Hypoglycemia Events

	35				36				37			
	IAsp	(n=708)	HI	(n=362)	IAsp	(n=597)	HI	(n=287)	IAsp	(n=91)	HI	(n=91)
# Event	n	%	n	%	n	%	n	%	n	%	n	%
0	597	**84.32**	297	**82.04**	492	**82.41**	232	**80.84**	82	**90.11**	86	**94.51**
1	66	**9.32**	39	**10.77**	53	**8.88**	32	**11.15**	6	**6.59**	3	**3.30**
2	17	**2.40**	10	**2.76**	24	**4.02**	7	**2.44**	3	**3.30**	1	**1.10**
3	10	**1.41**	7	**1.93**	11	**1.84**	5	**1.74**	0	**0.00**	1	**1.10**
≥4	18	**2.54**	9	**2.49**	17	**2.85**	11	**3.83**	0	**0.00**	0	**0.00**

The major hypoglycemic events in the first and last 3 months of the treatment period are displayed in Table 23.

Table 23 Major Hypoglycemic Events during the First & the Last 3 months of Treatment Period

Study	35				36				37			
	IAsp n=707		HI n=358		IAsp n=596		HI n=286		IAsp n=91		HI n=91	
First 3 Month	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Major A & B	80(11%)	193	37(10%)	88	78(13%)	141	42(15%)	105	5(5%)	6	4(4%)	5
Major A	74(10%)	168	28(8%)	74	68(11%)	123	39(14%)	96	5(5%)	6	4(4%)	5
Major B	11(2%)	25	11(3%)	14	15(3%)	18	5(2%)	9	0	0	0	0
Last 3 Month												
Major A & B	52(7%)	119	38(11%)	63	52(9%)	124	22(8%)	50	5(5%)	6	3(3%)	3
Major A	45(6%)	104	29(8%)	52	47(8%)	116	20(7%)	48	4(4%)	5	2(2%)	2
Major B	10(1%)	15	10(3%)	11	8(1%)	8	2(<1%)	2	1(1%)	1	1(1%)	1

n: number of subjects with major episode
E: number of episodes

Statistical Analysis on the Major Hypoglycemic Episodes

The sponsor conducted Cox regression on time to first major hypoglycemic episode. The relative risk of IAsp to HI with confidence intervals and p-value are displayed in Table 24.

Table 24 Analysis on Time to First Major Hypoglycemic Episode

Study	Relative Risk*	SE**	95% C. I.		p-value
# 35	0.85	(0.16)	(0.63,	1.16)	0.31
# 36	0.91	(0.17)	(0.66,	1.26)	0.56
# 37	1.78	(0.56)	(0.60,	5.32)	0.30

* Exponent of the coefficient
** Standard error of the coefficient

The major hypoglycemic episodes are recurrent events that may occur repeatedly over time. This reviewer conducted analysis that considered the multiple-event response. The results are displayed in Table 25.

Table 25 Analysis on Time to Recurrent Major Hypoglycemic Episodes

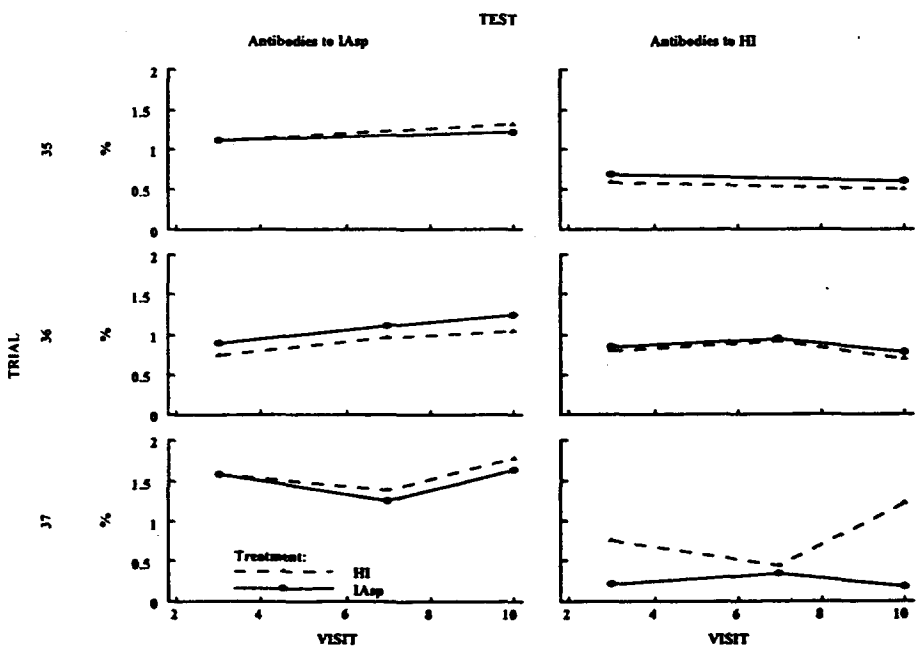
Study	Relative Risk*	SE**	95% C. I.		p-value
# 35	1.01	(0.05)	(0.78,	1.32)	0.91
# 36	0.90	(0.05)	(0.68,	1.19)	0.45
# 37	1.20	(0.23)	(0.67,	2.16)	0.54

* Exponent of the coefficient
** Standard error of the coefficient

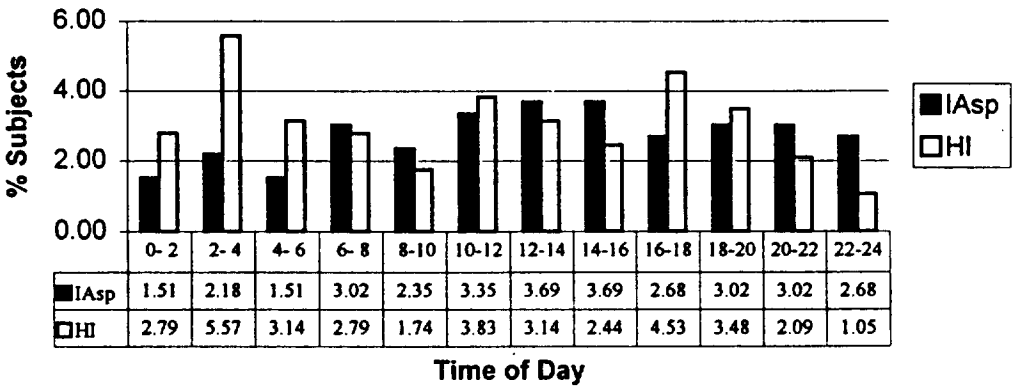
The confidence intervals of both analyses were consistent. But, the recurrent event analysis produced a tighter confidence interval. The sponsor pointed out that the p-values were not statistically significant between IAsp group and HI group.

The percentages of patients with ≥1 major hypoglycemia episodes over time of day are displayed in Figure 6 for studies 35, 36, and 37. In the early morning and 4 PM to 6 PM, a greater percentage of patients treated with HI experienced episodes of major hypoglycemia especially during 2 AM to 4 AM. At 8 to 10 AM and 12 to 4 PM, a greater percentage of patients in the IAsp treatment group experienced a major event.

Figure 6 Major Episodes vs Time of Day – Studies 35, 36, & 37

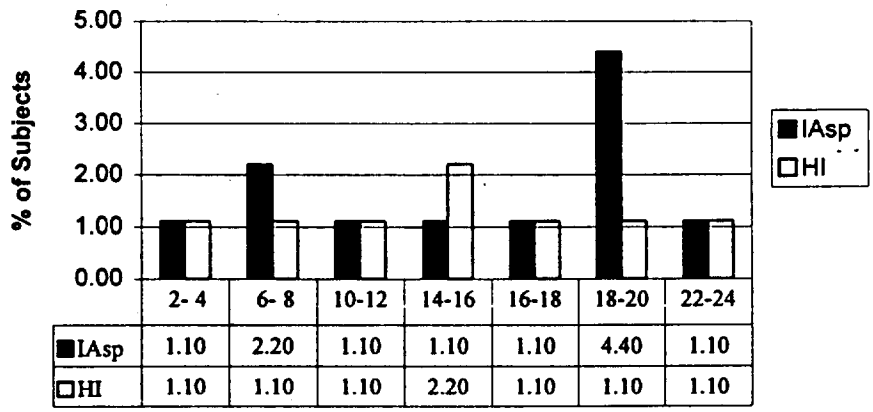


Study 36 - Major Episodes vs Time of Day



	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16	16-18	18-20	20-22	22-24
IAsp	1.51	2.18	1.51	3.02	2.35	3.35	3.69	3.69	2.68	3.02	3.02	2.68
HI	2.79	5.57	3.14	2.79	1.74	3.83	3.14	2.44	4.53	3.48	2.09	1.05

Study 37 - Major Episodes by Time of Day



	2-4	6-8	10-12	14-16	16-18	18-20	22-24
IAsp	1.10	2.20	1.10	1.10	1.10	4.40	1.10
HI	1.10	1.10	1.10	2.20	1.10	1.10	1.10

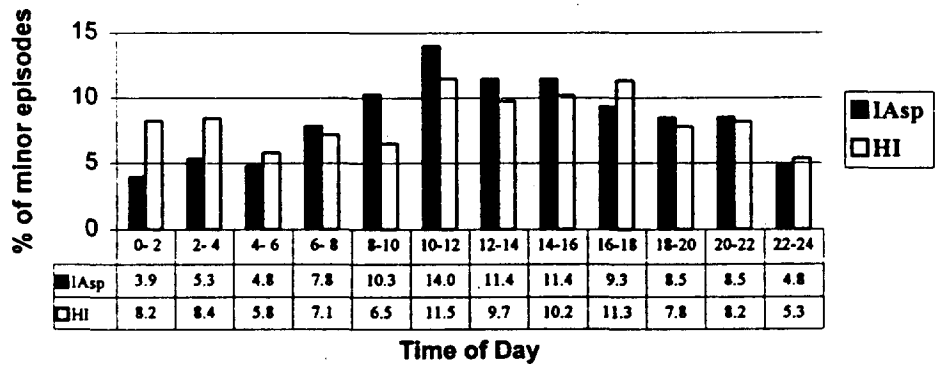
In study 37, the IAsp-treated patients experienced greater major events during time interval of 6-8 AM and 6PM-8PM where HI-treated patients experienced a greater major event during the time interval 2PM-4PM.

Minor Hypoglycemia Episodes

For studies 35 and 36, a majority of the minor hypoglycemic episodes were reported during the day. A greater percentage of minor hypoglycemic episodes were in the IAsp treatment group during the 5, 2-hour intervals from 6 AM to 4 PM, especially at 8-10 AM. From 4 PM to 6 PM and 0 to 6 AM, more hypoglycemic episodes occurred in the HI treatment group than the IAsp treatment group. A similar pattern was observed in study 37 as well (Fig 7).

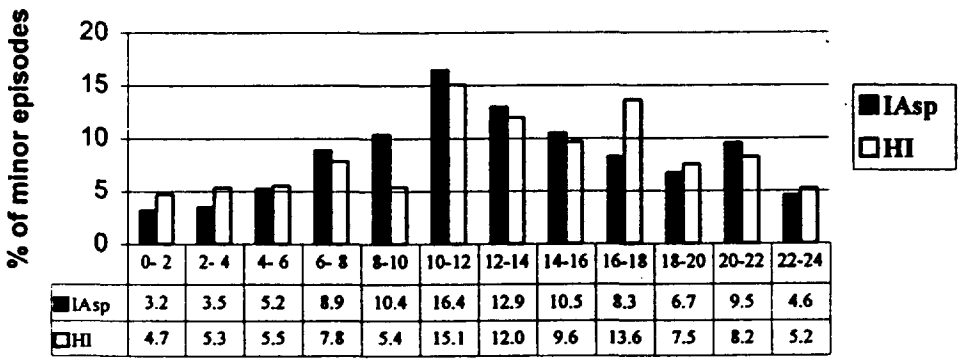
Figure 7 Minor Hypoglycemic Episodes by Time of Day – Studies 35, 36, & 37

Study 35 - Minor Episodes by Time of Day



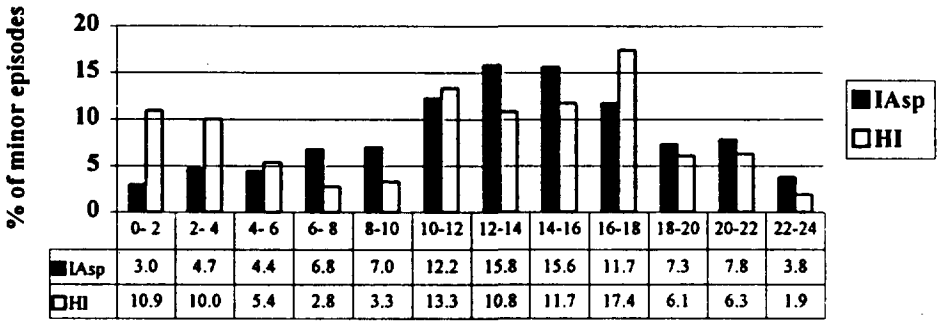
	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16	16-18	18-20	20-22	22-24
IAsp	3.9	5.3	4.8	7.8	10.3	14.0	11.4	11.4	9.3	8.5	8.5	4.8
HI	8.2	8.4	5.8	7.1	6.5	11.5	9.7	10.2	11.3	7.8	8.2	5.3

Study 36 - Minor Epidoses by Time of Day



	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16	16-18	18-20	20-22	22-24
IAsp	3.2	3.5	5.2	8.9	10.4	16.4	12.9	10.5	8.3	6.7	9.5	4.6
HI	4.7	5.3	5.5	7.8	5.4	15.1	12.0	9.6	13.6	7.5	8.2	5.2

Study 37 - Minor Episodes by Time of Day



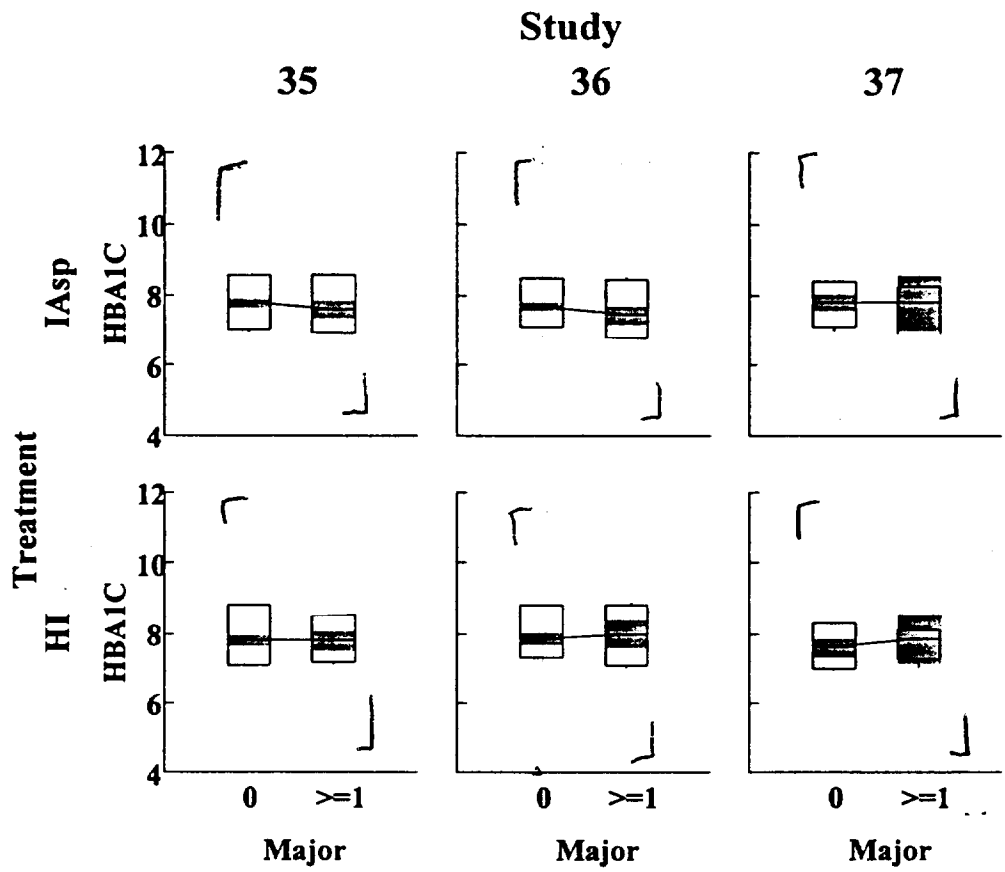
	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16	16-18	18-20	20-22	22-24
IAsp	3.0	4.7	4.4	6.8	7.0	12.2	15.8	15.6	11.7	7.3	7.8	3.8
HI	10.9	10.0	5.4	2.8	3.3	13.3	10.8	11.7	17.4	6.1	6.3	1.9

Major hypoglycemia events and HbA_{1c} level at month 6 were examined. Figure 6 displays the box plot of HbA_{1c} levels in patients with or without the major hypoglycemia events. In the IAsp-treated patients of studies 35 and 36, the HbA_{1c} level in mean and median appear lower in patients with hypoglycemia event than patients without the event. The descriptive statistics of HbA_{1c} levels in patients with or without a major hypoglycemia event are displayed in Table 26 and Figure 8.

Table 26 Descriptive Statistics of HbA_{1c} (%) at Month 6 in Patients with or without a Major Hypoglycemia

Trt	# Major	Study 35				Study 36				Study 37			
	Event	n	Mean	SD	Median	n	Mean	SD	Median	n	Mean	SD	Median
IAsp	0	582	7.88	1.21	7.8	472	7.80	1.08	7.7	80	7.87	1.19	7.8
	≥1	106	7.73	1.17	7.6	104	7.71	1.16	7.45	9	7.28	1.65	7.8
HI	0	282	8.01	1.37	7.8	218	8.03	1.15	7.85	81	7.69	1.09	7.6
	≥1	61	7.85	1.07	7.8	53	7.87	1.14	8.0	4	7.68	0.62	7.85

Figure 8 HbA_{1c} Levels at Month 6 by Major Hypoglycemia Events



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Antibodies

The descriptive statistics of specific and cross-reactive insulin antibodies are summarized in Table 27 and Figures 9 and 10 for Studies 35, 36 and 37 during the 6 months of treatment. In all 3 studies, the cross-reactive insulin antibodies increased from baseline in the IAsp treatment group but not in the HI group. The difference between treatments in change from baseline to month 6 was statistically significant in all three studies.

Table 27 Descriptive Statistics of Antibodies – Studies 35, 36, and 37

	Treatment													
Study Visit*	IAsp							HI						
	IAsp			HI		Cross		IAsp			HI		Cross	
S 035	n	Mean	SD	Mean	SD	Mean	SD	n	Mean	SD	Mean	SD	Mean	SD
3	702	1.12	3.51	0.69	3.20	12.24	14.02	357	1.11	3.97	0.58	1.70	10.98	13.13
10	676	1.21	3.27	0.60	3.14	16.92	15.76	340	1.30	4.05	0.49	1.77	10.99	13.30
S 036														
3	578	0.89	2.84	0.85	2.35	16.57	16.28	278	0.74	2.17	0.79	2.19	16.68	16.51
7	504	1.12	3.58	0.94	2.16	22.28	19.67	239	0.96	3.34	0.91	2.27	17.30	17.25
10	542	1.23	3.61	0.78	2.09	19.55	17.72	253	1.04	2.80	0.70	1.96	15.87	16.53
S 037														
3	89	1.58	4.18	0.21	0.71	11.03	16.57	90	1.59	5.49	0.75	5.61	9.72	14.71
7	84	1.25	3.47	0.33	0.63	13.94	18.79	80	1.39	5.28	0.44	1.96	9.27	13.54
10	87	1.63	4.22	0.18	0.62	14.06	17.50	82	1.79	6.71	1.23	6.76	8.10	13.08

*Visit 3=Baseline, Visit 7=Month 3, Visit 10=Month 6

Figure 9 The Cross-reactive Antibodies to Insulin during Treatment

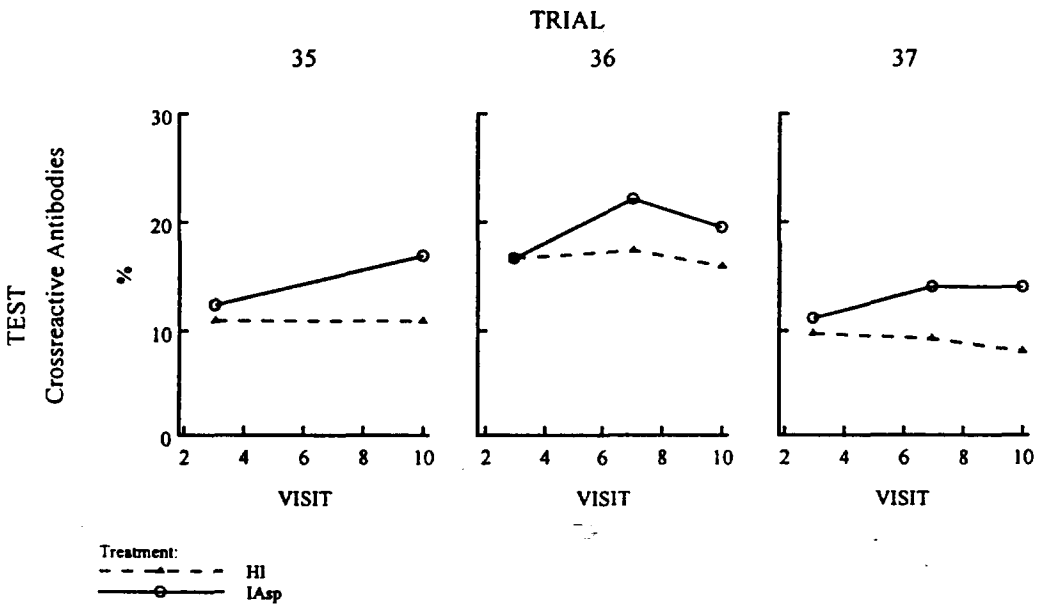

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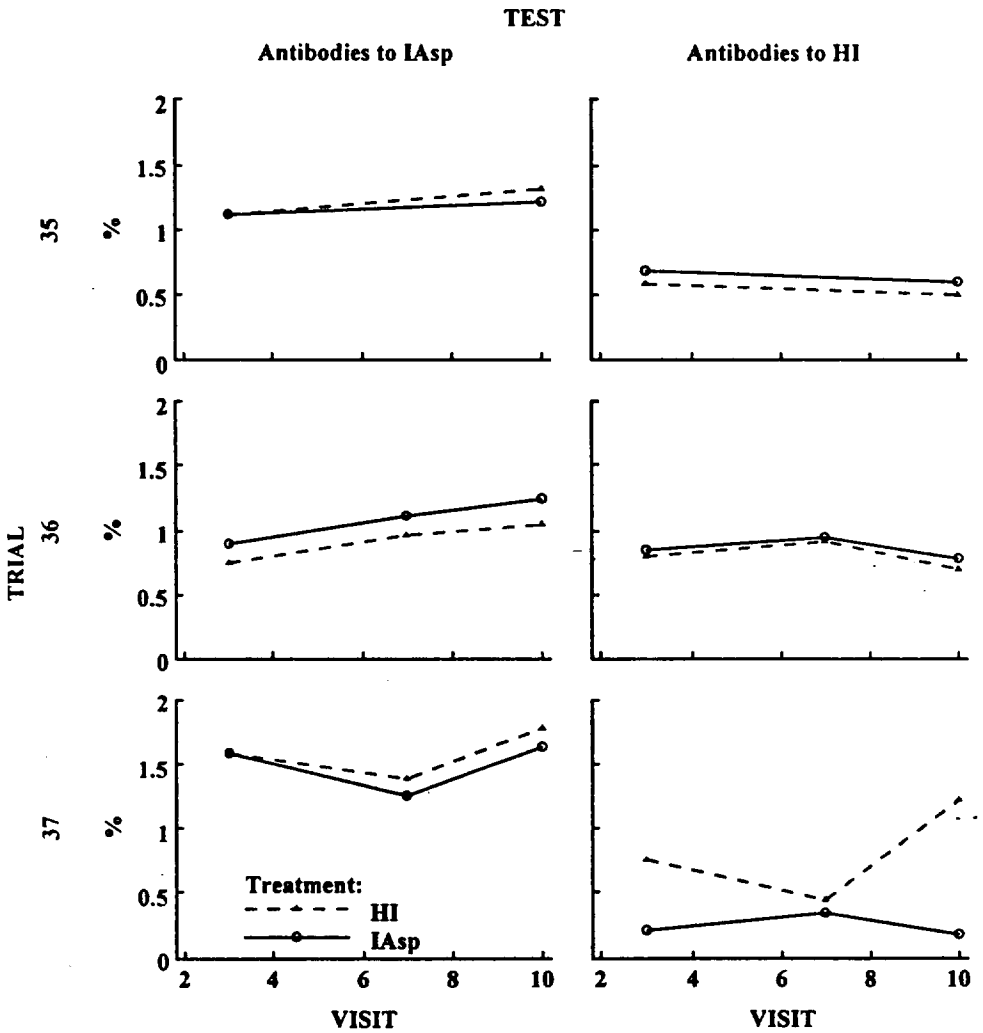
Figure 10 The Specific Antibodies to Insulin from Baseline to Month 6 – Studies 35, 36, & 37



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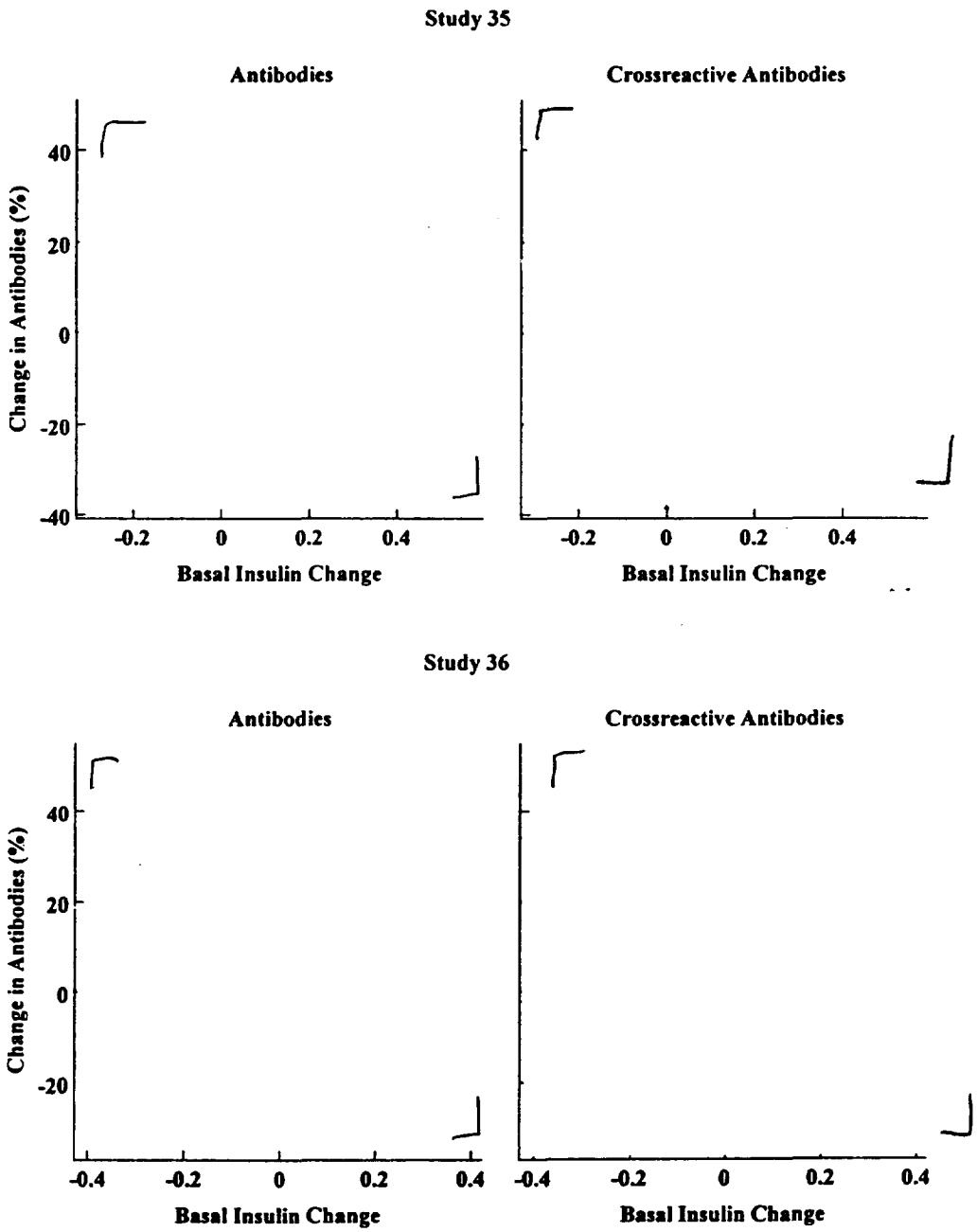
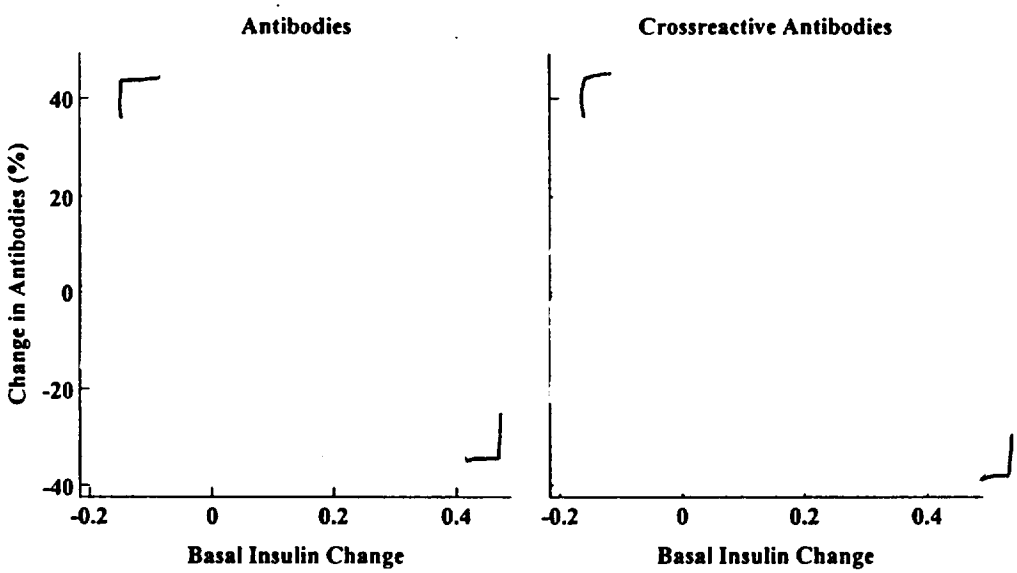
The increase of insulin dose was examined with the increase of the crossreactive antibodies. The sponsor concluded that the total insulin increase was not correlated with the increase of crossreactive antibodies. This reviewer used the basal insulin dose instead. Figure 11 plots the change in antibodies from baseline vs. the daily basal insulin change from baseline.

Figure 11 Antibody Levels by Basal Insulin Increase



Study 37



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Subgroup Analysis:

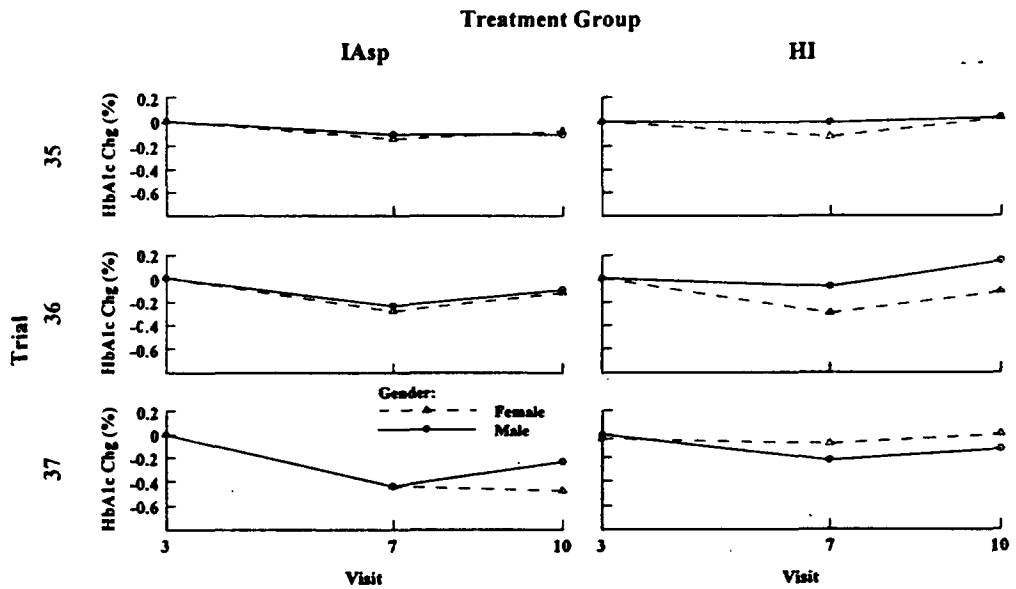
Descriptive statistics of change from baseline HbA_{1c} and basal insulin in subgroups of gender and age are summarized in the following tables and graphs for the per protocol population.

1. Gender

Table 28 Change from Baseline to Month 6 HbA_{1c} by Gender – Studies 35, 36, and 37

	Treatment					
Study	IAsp			HI		
S 035	n	Mean	SD	n	Mean	SD
Female	298	-0.08	0.75	146	0.02	0.86
Male	375	-0.11	0.82	184	0.03	0.77
S 036						
Female	263	-0.12	0.85	120	-0.12	0.84
Male	280	-0.10	0.82	137	0.14	0.80
S 037						
Female	29	-0.48	1.02	31	-0.01	0.94
Male	49	-0.24	1.01	47	-0.13	0.68

Figure 12 Change from Baseline HbA_{1c} by Treatment Group and Gender – Studies 35, 36 & 37



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The basal insulin increased more in males than in females in the IAsp treatment group (Table 29 & Figure 13). The descriptive statistics for meal plus basal insulin change is in Table 30.

Table 29 Change from Baseline to Month 6 Basal Insulin by Gender – Studies 35, & 36

	Treatment					
Study	IAsp			HI		
S 035	n	**Mean**	SD	n	**Mean**	SD
Female	299	**0.024**	0.057	147	**-0.005**	0.061
Male	375	**0.033**	0.070	185	**0.011**	0.066
S 036						
Female	265	**0.039**	0.085	120	**0.025**	0.083
Male	280	**0.056**	0.086	137	**0.025**	0.075

Figure 13 Change from Baseline Basal Insulin over Time by Gender – Studies 36 & 37

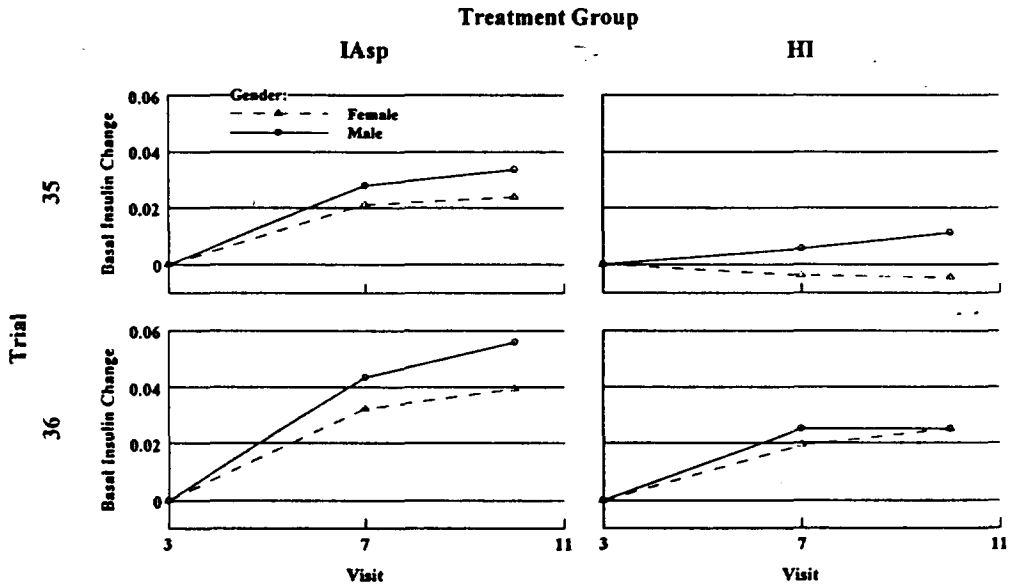


Table 30 Change from Baseline to Month 6 Basal±Meal Insulin by Gender – Studies 35, & 36

	Treatment					
Study	IAsp			HI		
S 035	n	**Mean**	SD	n	**Mean**	SD
Female	299	**0.011**	0.110	147	**-0.014**	0.128
Male	375	**0.023**	0.120	185	**0.008**	0.134
S 036						
Female	265	**0.033**	0.134	120	**0.010**	0.153
Male	280	**0.062**	0.129	137	**0.022**	0.120

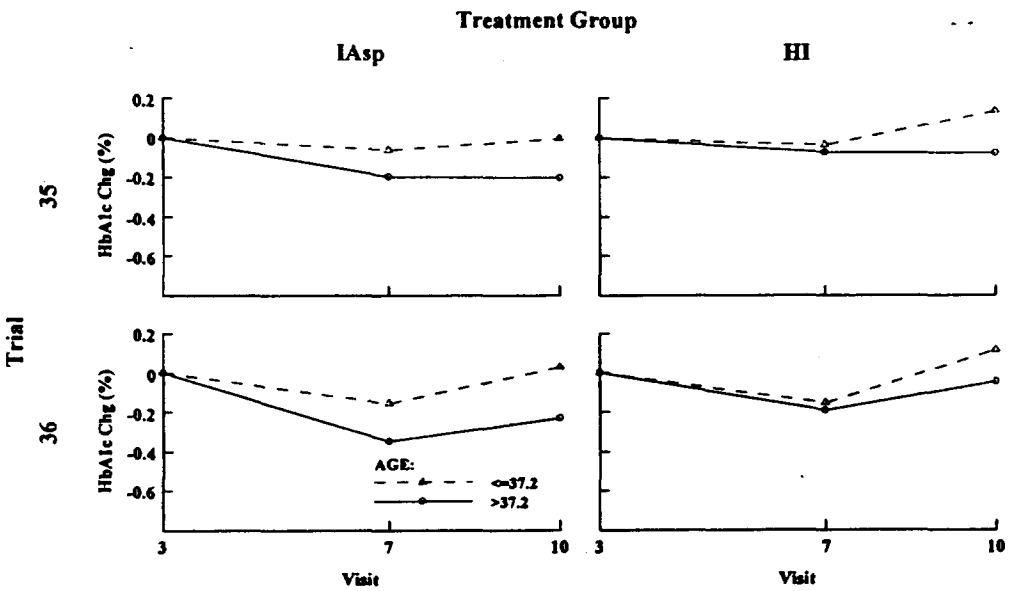
2. Age

For studies 35 and 36, the patients were grouped into less than or equal to the median age (37.2) and above the median age. The older patients had a greater reduction of HbA_{1c} than the younger patients (Table 31 & Figure 14). For type 2 diabetic patients (Study 37), the mean age was ~57 years.

Table 31 Change from Baseline to Month 6 HbA_{1c} by Age Group – Studies 35, 36, and 37

	Treatment					
Study	IAsp			HI		
S 035	n	Mean	SD	n	Mean	SD
≤ 37.2	365	-0.01	0.83	173	0.13	0.85
> 37.2	309	-0.20	0.73	159	-0.09	0.75
S 036						
≤ 37.2	252	0.03	0.84	110	0.10	0.81
> 37.2	293	-0.23	0.82	147	-0.04	0.84
S 037						
≤=57	39	-0.20	0.96	38	-0.11	0.87
>57	39	-0.45	1.05	40	-0.06	0.72

Figure 14 Change from Baseline HbA_{1c} over Time by Age Group – Studies 35, 36 & 37



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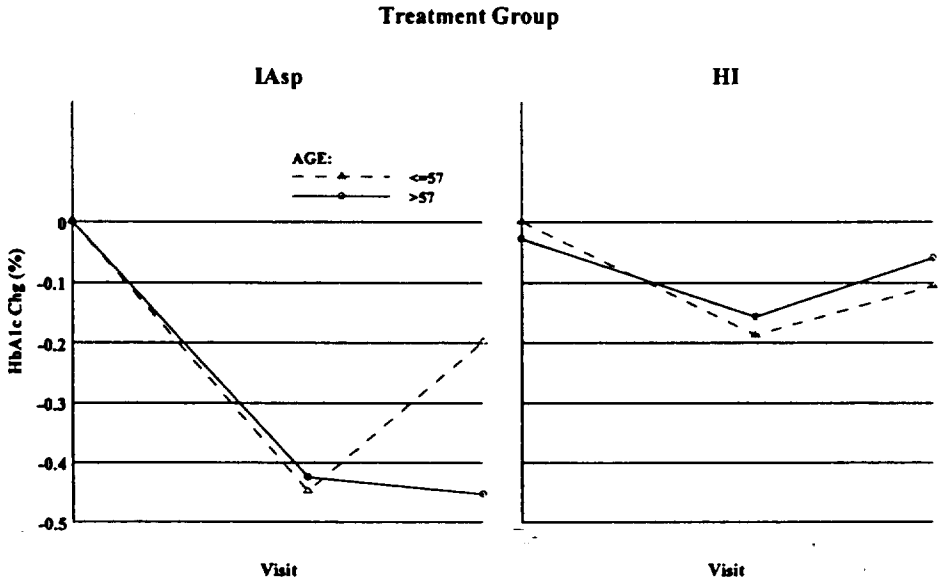
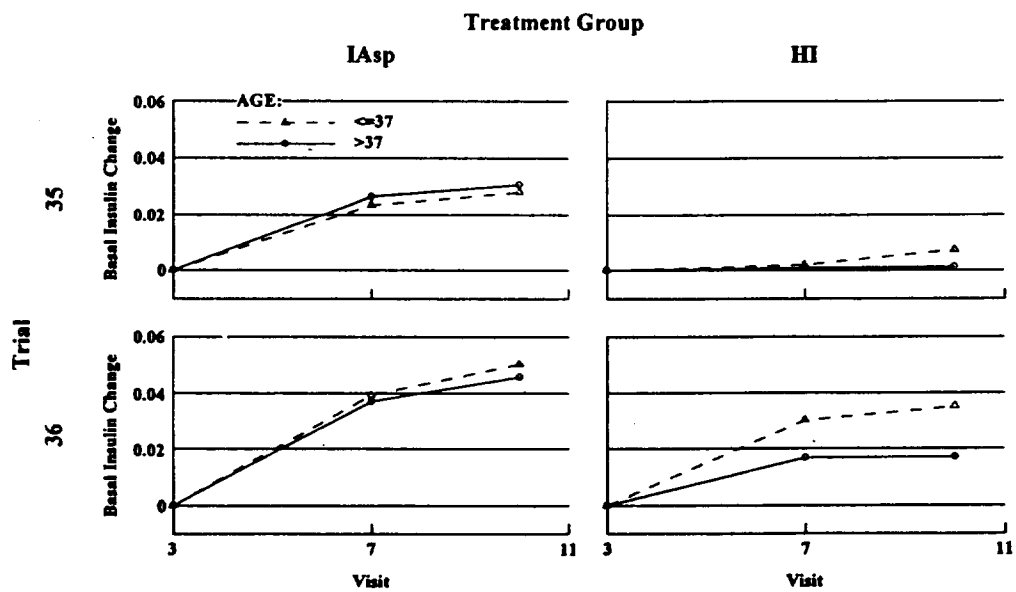
Trial 37



The basal insulin change from baseline to month 6 is displayed in Figure 15 for type 1 diabetic patients by age group (≤37 & >37).

Figure 15 Basal Insulin Change from Baseline by Visit and Age Group – Studies 36 & 37



Conclusion:

For the primary efficacy analysis of HbA_{1c} for non-inferiority of IAsp treatment to HI treatment at month 6, the upper confidence intervals of the differences in HbA_{1c} of IAsp and HI were within the prespecified "non-inferiority" margin of 0.6% for studies 35, 36 and 37. The estimates of the treatment difference and its upper confidence limits are -0.13 (-0.03), -0.16 (-0.05), and -0.09 (0.17) for studies 35, 36 and 37, respectively. Therefore, it is concluded that IAsp treatment is non-inferior to HI treatment in HbA_{1c}. The sponsor has claimed superiority of IAsp to HI in Type 1 patients (studies 35 & 36). This is unacceptable for several reasons. Not only is the treatment difference clinically insignificant but part of the observed treatment differences in Studies 35 and 36 could be attributed to the basal insulin dose increased in the IAsp group compared to the HI group. For hypoglycemic events in type 1 diabetic patients, there was no difference between the IAsp group and the HI group in the percentage of patients with at least one major event during the treatment.

/S/

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cc: Arch NDA 20-986
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